MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

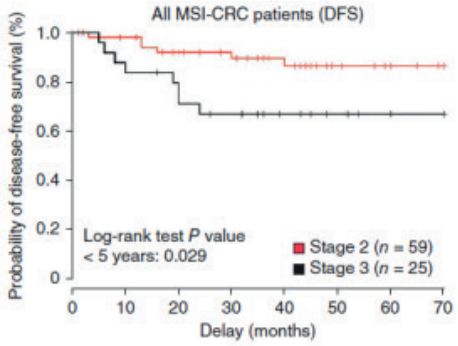
THERAPY

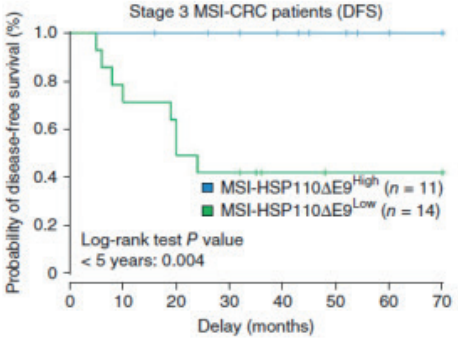
TRuTH110

TARGETED THERAPY OF HSP110 FOR CANCER THERAPY

CONTEXT & BACKGROUND

Colorectal cancer (CRC) is the second cause of cancer-related death world-wide. Two subtypes are classically defined to take into account tumor's molecular heterogeneity: microsatellite instable (MSI) and microsatellite stable (MSS). The MSI subtype is caused by a DNA mismatch repair (MMR) deficiency and represents about 15% of colorectal cancers. MSI patients present a higher number of tumor-infiltrating lymphocytes and have a better prognostic than MSS CRCs. We have: i) shown that MSI tumors universally harbor mutations in the heat shock protein HSP110 gene (Dorard et al., Nature Med. 2011) and ii) identified a mutation in a poly T intronic sequence that results in HSP110 exon 9 skipping and expression of a truncated protein, HSP110DE9, that constitutes an early marker of MSI CRCs patients (Patent 2011). HSP110DE9, the first HSPs mutant identified in a cancer so far, completely lacks HSP110 anti-apoptotic and chaperone activity. Further, it acts as a dominant negative that binds HSP110 and blocks its chaperone and oncogenic properties. In cultured colon cancer cells, mice xenografts and patients, HSP110DE9 expression sensitizes tumor cells to chemotherapeutic agents in a dose-dependent manner (Dorard et al., Nature Med. 2011).





INNOVATIVE COMPONENT & TECHNOLOGY

We propose a new target in cancer therapy: HSP110. Other HSPs are being targeted to sensitize cancer cells to chemotherapy.
For instance, many companies are developing inhibitors of HSP90 or HSP27 that are already in clinical trials. However, our last results convincingly demonstrate the interest and superiority or targeting HSP110 over the other HSPs. We have recently Maj mai 2016 published an important work demonstrating the rationale for such an approach: only colon cancer patients that respond to the chemotherapy express an endogenous specific inhibitor of HSP110 (HSP110DE9). This association between the inactivation of HSP110 and good prognosis was demonstrated in a multicentre study including more than 5,000 patients (Collura et al., Gastroenterology 2014). We have also demonstrated that HSP110DE9 was a dominant negative mutant that binds to wild type HSP110 and inhibits the chaperone activity of HSP110; HSP110 is a very important chaperone in cancer cells since not only it has an anti-aggregation activity by its own but also acts as a co-chaperone (nucleotide exchange factor) for other HSPs like HSP70. Therefore by blocking HSP110, the chaperones network in the cell is strongly perturbed as we have already reported (Dorard et al., Nat Med 2011).

SCOPE

Initially : colon cancer patients

KEYWORDS

Targeted therapy, Heat shock Protein 110, small molecules, peptide mimetics

OBJECTIVES

To take advantage of the HSP110DE9 chemosensitizing effect in cancer therapy. We have identified and are developing biologics as well as small molecules inhibitors of HSP110 that mimic the anti-cancer effect of HSP110DE9 and that we could test in phase I clinical trials (with the anticancer center: Centre Georges-François Leclerc (CFGL) in Dijon).

DEVELOPMENT & MATURATION STAGE

Confirmation and characterization of hits as well as ongoing structural studies.

TARGET POPULATION

Initially colon cancer patients (both of the type microsatellite instable, MSI, and stable, MSS). Colorectal cancers are very frequent tumors (e.g.: 150,000 new cases in 2012 only in the U.S.). This major oncological issue would benefit from the present project. Moreover, several other types of cancers should also benefit from this chemo-sensitizing therapy since, by administrating an inhibitor of HSP110, they would become “MSI-like-chemo-sensitive”.

TARGET PROFILE

Not disclosed.

STRENGHTS & COMPETITIVE ADVANTAGES

- Originality and importance of the target
- International and national expertise in HSPs and MSI fields
- Multidisciplinary consortium and translational research
- Top quality of scientific output and collaborative network
- HSP110 is a brand new target in cancer

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

Colorectal cancer is the second most common cause of cancer-related death worldwide (~6700,000 deaths, WHO 2012). A significant fraction (15%) of this molecularly heterogeneous disease shows widespread genetic instability at DNA repeats, due to a defective mismatch repair system. In 2009 for example, the small-molecule drugs constituted 23% (~$2.4 billion) of the total US sales — the largest pharmaceutical market — of targeted therapies (the aim of the present project). The targeted market is large and attractive.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

We foresee several patents (and publications) provided by independent workpackages. New therapeutic strategies may emerge from this project.

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